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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,826	07/21/2005	Viktor Menart	LB/G-32991A/LEK	4902
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SANDOZ INC 506 CARNEGIE CENTER PRINCETON, NJ 08540			EXAMINER MACFARLANE, STACEY NEE	
			ART UNIT	PAPER NUMBER
			1649	
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			06/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/522,826

Applicant(s)

MENART ET AL.

Examiner

STACEY MACFARLANE

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Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 February 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7, 10, 12-17, 19-21, 23-27 and 29-31 is/are pending in the application.
- 4a) Of the above claim(s) 2, 27 and 29-31 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3-7, 10, 12-17, 19-21 and 23-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Response to Amendment

1. Claims 1, 3-7, 10, 12-17, 19-21 and 23-26 have been amended, Claims 8, 9 and 22 are cancelled, as requested in the amendment filed on February 27, 2008. Following the amendment, claims 1, 2-7, 10, 12-17, 19-21, 23-27 and 29-31 are pending in the instant application.

Claims 2, 27 and 29-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant elected without traverse in Paper filed on August 24, 2007.

Claims 1, 3-7, 10, 12-17, 19-21 and 23-26, in so far as they read upon the elected species G-CSF, are under examination in the instant office action.

2. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3. Applicant's arguments filed on February 27, 2008 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

New Grounds of Rejections/Objections, Necessitated by Amendment

Claim Objections

4. Claims 2, 27, 29-31 are objected to because of the following informalities: The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any withdrawn subject matter must be shown, as set forth in 37 CFR 1.121(c). Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 3-7, 10, 12-17, 19-21 and 23-26 are rejected under 35 U.S.C. 112, second paragraph, for reasons of record in the Paper filed September 27, 2007.

7. Claim 1, as currently amended, is vague and indefinite in its recitation of "having an aqueous solubility in the cells". The claim is missing an essential element within the method that specifically relates the solubility of the inclusion bodies of the claim to the alteration of the parameters. Absent said element the inclusion bodies of the invention are indistinguishable from "classical inclusion bodies" within the art and it potentially raises issues as to how one of ordinary skill in the art affects the solubility of the inclusion bodies, and how one of skill in the art would determine the requisite degree of solubility. The issue is rendered further unclear with the additional requirements for

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further "solubilizing the inclusion bodies", which were already stated as being soluble, and a washing step comprising contacting the inclusion bodies with "a solution", when they are presumably already in solution. Therefore, one of ordinary skill in the art would not be reasonably apprised as to metes and bounds of the claims.

8. Claim 1 is further vague and indefinite in its recitation of "induction mode", "principle of performing the fermentation" and an agent "capable of causing stress". One of ordinary skill in the art would not be able to ascertain the metes and bounds of the invention as claimed.

9. Claims 3-7, 10, 12-17, 19-21 and 23-26 are indefinite for depending from indefinite claims.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. As currently amended, Claims 1, 3-6, 12-15, 17, 23, 24 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Heidari et al., *Veterinary Immunology and Immunopathology*, 81:45-57, published August 2001 (hereafter "Heidari").

12. Claim 1 is drawn to a process for the production of a biologically active protein comprising the active steps of expressing said protein as a heterologous protein in an

expression system, regulating one or more cultivation parameters wherein the aqueous solubility of the inclusion bodies is affected, isolating the inclusion bodies (IB), optionally washing them, solubilizing them under non-denaturing conditions, and purifying the biologically active protein. Dependent claims recite: wherein the heterologous protein is the instantly-elected G-CSF (claims 3 and 4); the expression system is *E. coli* bacteria (claims 5 and 6); wherein the inducer is IPTG (claims 12 and 13); wherein the concentration of IPTG is from about 0.1 mM to about 1 mM (claims 14 and 15); wherein the fermentation consists of performing fermentation in batch mode, in fed batch mode, or in one or more shake flasks (claim 17); wherein the step of washing comprises contacting the inclusion bodies with a solution consisting of phosphate buffer (claim 23); wherein the concentration of the selected buffer ranges from about 1 mM to about 10 mM (claim 24); and wherein a nondenaturing solution comprises N-lauroylsarcosine (claim 26).

13. The Heidari prior art teaches a method of producing G-CSF (abstract) comprising expressing a heterologous protein in *E. coli* (sections 2.1 and 2.2 pages 46-47). The Heidari reference teaches regulation of several parameters, such as the principle of performing the fermentation (in one or more shake flasks), temperature, mode of induction by 1 mM IPTG, etc. (section 2.2, page 47). The reference then teaches isolating the inclusion bodies, and washing several times with PBS (section 2.3), in which phosphate buffer is typically "about 10 mM" as required by claim 24. Heidari et al., further teach solubilizing the inclusion bodies under non-denaturing conditions, specifically, by contacting the inclusion bodies with sarkosyl, commonly known in the art

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as N-lauroylsarcosine (claim 26). While the reference teaches contacting the IB with a 2% sarkosyl, and the claims state "about 0.05% to about 0.25% mass per volume", discrepancies in ranges of compositions are deemed inherent based on what would result due to optimization of conditions MPEP 2112. The burden of proof rests upon the Applicant to demonstrate that the concentration as taught by the prior art does not necessarily or inherently possess the characteristics of Applicant's claimed invention. Furthermore, the Heidari prior art specifically teaches that the G-CSF produced is biologically active (abstract), however, even if the reference were silent on this aspect the Heidari art teaches all of the active steps required by the claim to produce protein and therefore biological activity would be inherent. The instant method does not distinguish over the prior art.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

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3. Resolving the level of ordinary skill in the pertinent art.
 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
14. Claims 1, 3-7, 10, 12-17, 19-21 and 23-26 rejected under 35 U.S.C. 103(a) as being unpatentable over Heidari et al. (2001) as applied to claims 1, 3-6, 12-14, 17, 23 and 24 above, and further in view of Carrió and Villaverde, *Journal of Biotechnology*, 96: 3-12, published June 13, 2002.

The Heidari prior art teaches a method of producing biologically active G-CSF (abstract) comprising expressing a heterologous protein in *E. coli* (sections 2.1 and 2.2 pages 46-47). The Heidari reference teaches regulation of several parameters, such as the principle of performing the fermentation (in one or more shake flasks), temperature, mode of induction by IPTG, etc. (section 2.2, page 47). The reference then teaches isolating the inclusion bodies, and washing several times with PBS (section 2.3), in which phosphate buffer is typically "about 10 mM" as required by claim 24. Heidari et al., further teach solubilizing the inclusion bodies under non-denaturing conditions, specifically, by contacting the inclusion bodies with sarkosyl, commonly known in the art as N-lauroylsarcosine.

The Heidari reference fails to explicitly teach the regulation of alternating cultivation parameters such as composition of medium (claims 1, 19 and 20), agents capable of causing stress (claims 1 and 21), co-expression of auxiliary proteins (claim 1).

The Carrió and Villaverde reference fulfills the deficits of the Heidari reference by teaching that it was well-known in the art, prior to filing, that several factors affect the

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solubility of inclusion bodies and the subsequent yield of biologically active and correctly folded recombinant protein upon expression in bacteria. Specifically, the Carrió and Villaverde reference teaches the simultaneous co-expression of chaperone-encoding genes, as well as temperature regulation and manipulation of media composition improves the solubility (page 4, last paragraph). Importantly, Carrió and Villaverde teach that it was known in the art that IBs are a convenient source of relatively pure target polypeptide (page 5, lines 3-4 and page 6, line 1 as bullet 3), and that at least an important fraction of IB protein remains suitable for correct folding and biological activity (paragraph bridging pages 5-6). Furthermore, any discrepancies between the media or reagents of the claims and those of the references are deemed to be *prima facie* obvious based on optimization of a known process, or at least an obvious variant by substitution of a known prior art element (See *KSR*, at 1742, 82 USPQ2d at 1390, citing *Dystar* 464 F.3d at 1368, 80 USPQ2d at 1651).

Where the products produced by the claimed method and those produced by the prior art method are identical or substantially identical, a *prima facie* case of either anticipation or obviousness has been established and the burden of proof rests upon the Applicant to demonstrate that the prior art does not necessarily or inherently possess the characteristics of Applicant's claimed product. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the

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burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Double Patenting

15. It stands that if claim 3 should be found allowable, claim 4 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof, in view of Applicant's election of G-CSF species in the Response to Election/Restriction filed July 24, 2007. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

16. No Claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M,W and ALT F 7 am to 3:30, T & R 5:30 -5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
Art Unit 1649

/Olga N. Chernyshev, Ph.D./
Primary Examiner, Art Unit 1649